

Remarks

Summary

Claims 1-5, 10, 11, 14-16, 19-29, 36-40 and 47-66 are currently pending. Claims 1-5, 10, 11, 14-16 and 19-29 are withdrawn as required by a previous restriction. Claims 36-39, 47, 48, 49, 51, 53 and 58 are currently amended. Claims 50, 52, 54-57 and 59-66 are previously presented. Claim 40 is original. Applicants add new claims 67 and 68. Support for the subject matter of the newly added claims is found throughout the specification. No new matter has been entered.

Claims 36-40 and 47-66 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 36-38 and 40 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Manger et al.

Claims 36, 47-51, 53-55 and 58-59 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Zhu et al.

Claim 39 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Manger et al., as applied to claim 36, in view of Brown et al.

Claims 52 and 60-66 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Zhu et al. in view of Braun further in view of Brown et al.

Claims 56 and 57 are rejected 35 U.S.C 103(a) as allegedly unpatentable over Zhu et al. in view of Glezer et al.

The invention, among other things, provides systems and methods for automatic identification of multiple pathogens, including unsequenced and uncataloged or unknown species. The invention provides pathogen identification via the combined use of cultured cells as hosts, the reliance on the in vitro expression patterns of these cell hosts during an in vitro encounter with pathogenic agents, microarray-based sensing, machine learning and microarray pattern recognition for automatic identification, and the use of information fusion methods (for exploitation of all, or substantially all, available information and multiclassifier techniques, as well as the potential for using multiple host cell types and microarray types).

Information Disclosure Statement

The Examiner alleges that the Information Disclosure Statement filed on August 5, 2004 (not on August 5, 2005 as indicated in the Office Action) fails to comply with 37 CFR 1.98(a)(2). Specifically, the Examiner alleges that a copy of Delehanty et al. was not received. To assist the Examiner in considering this reference, Applicants enclose herewith a courtesy copy of Delehanty et al. Applicants request consideration of this reference.

Applicants note, however, that no fee is due upon submission of Delehanty et al. Applicants' Information Disclosure Statement and form PTO 1449 were timely filed prior to the mailing of the first office action. Delehanty et al. was listed on these forms. Furthermore, Applicants' itemized postcard indicated that the cited references were included with the materials sent to the US Patent Office on August 2, 2004. These materials create a presumption that the references were submitted by Applicants and received by the Patent Office. If these materials do not create such a presumption, then they would cease to perform any useful administrative function for either the Patent Office or Applicants.

Rejections under §112

Claims 36-40 and 47-66 are rejected under 35 U.S.C. 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

(a) Claim 36 is rejected as allegedly vague because the preamble of the claim recites a method for identifying the presence of a pathogenic agent while the body of the claim does not recite identification of a pathogenic agent. Applicants' amendment to claim 36 is believed to obviate this rejection.

The Office Action further states that the phrase "disparate types of biological data" is unclear because it is allegedly vague as to what kind of biological data is collected. Applicants use the phrase "disparate types" to indicate the broad scope of biological data that may be collected and used in practicing the methods of the present invention. The invention benefits from the ability to utilize biological data of many different types (e.g., modalities). The use of varying types of biological data is exemplified throughout the specification. (*See*, for example, page 7, lines 13-23). Applicants further note that Webster's Dictionary defines "disparate" as being dissimilar and containing dissimilar components. Accordingly, Applicants contend that

the term disparate is clear based on the specification and its commonly understood definition, and thus that one of skill in the art can readily appreciate the metes and bounds of the claimed subject matter.

Nevertheless, to expedite prosecution, Applicants have amended the claim to delete reference to the term "disparate." Applicants' amendment is made solely for clarity and does not narrow the scope of the claim which encompasses the use of any of a wide range of biological data. Applicants' amendment is believed to obviate the rejection, and reconsideration and withdrawal is requested.

(b) Claims 36 and 37 were rejected because recitation of "the same" allegedly lacks proper antecedent basis. Applicants' amendments are believed to obviate the rejection.

(c) With regard to claim 38, the Office Action states that it is unclear whether employed microarrays comprise one set of probes or whether employed microarrays comprise one set of probes per each microarray. To clarify that which is claimed, Applicants have amended claim 38 to recite "at least one microarray each having at least one set of probes".

(d) With regard to claim 39, the Office Action states that there is insufficient antecedent basis for "the pathogen" in lines 2-3 of the claim. To improve the clarity of the claim, Applicants have amended claim 39 to replace "the pathogen" with "the pathogenic agent". Applicants note, however, that the terms "pathogen" and "pathogenic agent" are used interchangeably in the art. Pathogens are typically defined as infecting agents that cause diseases. Accordingly, Applicants' amendment to claim 39 does not narrow the scope of the claim.

(e) Claim 47 is rejected for allegedly lacking correlation between the preamble of the claim and the steps of the claimed method. Claim 47 was further rejected for being vague and lacking sufficient antecedent basis for recitation of "the measured" in line 8. Applicants' amendments to claim 47 are believed to obviate each of these grounds of rejection.

(f) With regard to claims 48 and 49, the Office Action alleges that the claims lack correlation between the preamble and the recited method steps. The Office Action further alleges that recitation of "said plural biological responses" lacks proper antecedent basis, and is thus unclear.

Applicants contend that claims 47 to 49 are clear and that one of skill in the art can readily ascertain the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims to improve their clarity. Applicants'

amendments are made solely for clarity and do not narrow the scope of the claims. Applicants' amendments are believed to obviate the rejection, and reconsideration and withdrawal of this rejection are requested.

(g) With regards to claims 50 and 51, the Office Action states that the claims recite the phrase "substantially all," which allegedly is vague because it is unclear what amount of measured biological response data is required to encompass substantially all of the measured data. Applicants respectfully disagree with the Examiner's assertion. Typically, in the art, measured biological response data includes the "most relevant" portions of data from the microarrays. Applicants point out that the knowledge of "relevance" of data may be questionable or even unavailable. The invention circumvents the issue of relevance by including a larger dataset of biological data. Applicants recite the phrase "substantially all" in order to clarify the quantity of data used to include a larger dataset of information obtained from microarrays and other molecular phenomena and products (*See*, for example, page 6, para 2, lines 10-22). In light of these remarks, Applicants believe that the phrase "substantially all" is of sufficient clarity. Reconsideration and withdrawal of this rejection is requested.

(h) Claim 53 is rejected because recitation of "high virulence is vigorous" is allegedly vague. Applicants' amendment to claim 53 is believed to improve the clarity of the claim and to obviate the rejection. Reconsideration and withdrawal of the rejection is requested.

(i) Claim 58 is rejected because recitation of "and/or" is allegedly vague. Applicants' amendment to claim 58 is believed to improve the clarity of the claim and to obviate the rejection. Reconsideration and withdrawal of the rejection is requested.

(j) The Office Action alleges that using subspace measures of fitness in claim 65 is vague because it is unclear for what the subspace measures of fitness are used. Applicants respectfully disagree with the Examiner's assertion regarding the clarity of the use of the subspace recognizer measures of fitness. Applicants contend that the use of these terms is clear in light of the specification that describes subspace measures of fitness, as well as the use of recognizer results for generating an identification of a test pattern (*See*, for example, page 11, par. 3, lines 1-4). Accordingly, Applicants contend that one of skill in the art can readily appreciate the metes and bounds of the claim 65. Reconsideration and withdrawal of this rejection is requested.

Rejections under §102(b)

Claims 36-38 and 40 as rejected under 35 U.S.C. 102(b) as allegedly anticipated by Manger et al. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

To anticipate, a single prior art reference must teach or suggest each and every limitation of a presently claimed invention. Manger et al. fail to satisfy these criteria, and thus Manger et al. fail to undermine the patentability of claims 36-38 and 40.

The Office Action states that Manger et al. teach a method for identifying the presence of a pathogenic agent. Applicants respectfully disagree with the Examiner's assertion. Manger et al. merely teach gene expression responses to infection. In essence, Manger et al. merely observe the way in which host cells respond to infection. In contrast, the methods of the present invention permit the identification of a pathogenic agent based on analysis of the pathogenic signature generated upon infection of host cells with the pathogenic agent. Thus, the present invention provides methods for identifying pathogens. Such methods are different from and neither taught nor suggested by observations of host cells following infection by a pathogen, as disclosed by Manger et al.

Additionally, Manger et al. fail to teach or suggest the use of information fusion to process the biological response. Manger et al. do not disclose "fusion" of information. Instead, Manger et al. disclose the "clustering" of information. The Examiner appears to have interpreted the term "information fusion" to simply mean the technique of comparing two or more sets of information. Applicants argue that "information fusion" is a term of art in computer science and artificial intelligence and requires a deeper and fairer interpretation. In essence, information fusion involves combining multiple sources of data and making them work together to solve a problem or perform a recognition task. More generally, information fusion is an artificial intelligence methodology that enables computers to make decisions (e.g., conceptually similar to the way in which humans would make decisions) in situations where the sufficient information may not be available. The ability of an exemplary information fusion technique to enable decision-making based even on insufficient data helps differentiate it from a simplistic data comparison technique. In light of the above remarks, Applicants argue that Manger et al. do not employ methods using information fusion, as recited in independent claim 36. Accordingly, Manger et al. fail to anticipate the claimed invention.

Nevertheless, to expedite prosecution, Applicants have amended claim 36, and claims dependent thereon, to more particularly point out the claimed method. Specifically, Applicants have amended claim 36 to more particularly point out that the claimed method is a method of identifying a pathogenic agent. Such a method of identifying a pathogenic agent, and not merely observing a response to an infection, is neither taught nor suggested by Manger et al. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' amendments, reconsideration and withdrawal of this rejection is requested.

Rejections under §102(e)

Claims 36, 47-51, 53-55 and 58-59 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Zhu et al. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

To anticipate, a single prior art reference must teach each and every limitation of the presently claimed invention. Zhu et al. fail to satisfy these criteria, and thus Zhu et al. fail to undermine the patentability of claims 36, 47-51, 53-55, and 58-59.

The Office Action states that Zhu et al. teach the step of employing information fusion to process the biological response. More specifically, the Office Action asserts that Zhu et al. disclose fusing the information from the test sample and the control sample. Applicants respectfully disagree with the Examiner. Firstly, Zhu et al. do not disclose "fusion" of information. Instead, Zhu et al. disclose the "comparison" of information from a test sample with information from a control sample for the purposes of providing a measure of relative expression of the nucleic acids (*See* Par. 0114). The Examiner appears to have interpreted the term "information fusion" to simply mean the technique of comparing two or more sets of information. Applicants argue that "information fusion" is a term of art in computer science and artificial intelligence and requires a deeper and fairer interpretation. In essence, information fusion involves combining multiple sources of data and making them work together to solve a problem or perform a recognition task. More generally, information fusion is an artificial intelligence methodology that enables computers to make decisions (e.g., conceptually similar to the way in which humans would make decisions) in situations where the sufficient information may not be available. The ability of an exemplary information fusion technique to enable decision-making based even on insufficient data helps differentiate it from a simplistic data

comparison technique. In light of the above remarks, Applicants argue that Zhu et al. do not disclose any aspects of information fusion as recited in independent claim 36 and therefore reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action further asserts that Zhu et al. teach the step of applying machine learning processes to the plural biological responses to identify a pathogenic signature. More specifically, the Office Action states that Zhu et al. obtain a control signature to analyze a test signature. Applicants respectfully disagree with the Examiner's assertion. Zhu et al. do not disclose the step of applying "machine learning" as recited in claim 47-66. "Machine learning" is a term of art in computer science and artificial intelligence that involves automatic learning from data. Machine learning typically includes a method by which a computer can create and modify the system's operation (e.g., its behavior and the results it produces) by processing data. Machine learning enables a computer to learn from the process of analyzing data and to modify system's operation and behavior in response to data. In other words, machine learning consists of algorithms that learn automatically. Zhu et al. do not teach or suggest applying machine learning processes as recited in claims 47-66. Accordingly, Zhu et al. fail to anticipate the claimed invention, and reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action also states that Zhu et al. teach a method for identifying the presence of a pathogenic agent. Applicants respectfully disagree with the Examiner's assertion. Zhu et al. disclose methods, compositions and apparatus for studying the complex regulatory relationships among host genes and viruses, in particular HCMV. In specific applications, Zhu et al. provides methods for identifying drugs for preventing or ameliorating disease symptoms caused by HCMV, determining the stage of infection or extent of tissue damage caused by HCMV infection, and a general method for narrowing large sets of genes to a smaller subset based on relevance. Zhu et al. do not teach or suggest a method for identifying a pathogenic agent as required by independent claim 36.

Applicants contend that Zhu et al. fails to anticipate the presently claimed invention. Zhu et al. fails to teach or suggest "information fusion" or "machine learning", as required by the presently claimed methods. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections under §103(a)

Claim 39 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Manger et al. in view of Brown et al. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

As outlined in detail above, Manger et al. fail to anticipate the claimed invention. Specifically, Manger et al. fail to teach or suggest methods of identifying a pathogenic agent. Brown et al. fail to overcome the deficiencies of Manger et al. Reconsideration and withdrawal of this rejection is requested.

Claims 52 and 60-66 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Zhu et al. in view of Braun and further in view of Brown. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

As outlined in detail above, Zhu et al. fail to anticipate the claimed invention. Specifically, Zhu et al. fail to teach or suggest a method of identifying a pathogenic agent using either information fusion and/or machine learning. Braun and Brown fail to overcome these deficiencies for several reasons.

First, Zhu et al. merely teach a method for comparing information from test sample probes with information from control sample probes to measure the relative expression of the nucleic acids that hybridize to each of the probes. Zhu et al. fail to teach a method for identifying a pathogenic agent using information fusion and/or machine learning. These deficiencies of Zhu et al. are not overcome by references such as Braun and Brown. Specifically, these isolated references teaching particular mathematical and computational models and techniques for machine learning do not teach one of skill in the art how to apply these tools to the problem of identifying pathogenic agents.

Second, absent Applicants' disclosure, one of skill in the art would not have been motivated to combine the teachings of Zhu et al. with the teachings of Braun or Brown. As noted above, Zhu et al. does not teach or suggest utilizing information fusion or machine learning in the context of pathogen identification or in the context of analyzing biological data. Absent such a suggestion, the skilled artisan in the biological sciences would not have been motivated to combine the mathematical teachings provided by the Braun or Brown references with the teachings of Zhu et al. Zhu et al. does not teach or suggest bringing the powerful mathematical and computational methods, for example the methods taught by the Braun reference, to bear on the problem of processing biological data to identify pathogenic agents.

Braun does not teach or suggest the application of information fusion and machine learning methodologies to biological systems. Accordingly, there is no motivation, absent Applicants' disclosure, to combine these references. In accordance with MPEP 2143.01 and with case law, "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP 2143.01; *See, In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000); *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992).

The combination of Zhu et al., Braun, and Brown fail to render the claimed invention obvious. The combination of references fails to teach or suggest the claimed invention. Furthermore, absent the present application, one of skill in the art would not have been motivated to bring the mathematical and computational analysis of Braun and Brown to bear on the problem of identifying and characterizing host-cell responses to pathogenic agents. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 56 and 57 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Zhu et al. in view of Glezer et al. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

As outlined in detail above, Zhu et al. fail to undermine the patentability of the claimed invention. Glezer et al. fail to overcome the deficiencies of Zhu et al. Accordingly, reconsideration and withdrawal of this rejection is requested.

CONCLUSION

Applicants believe no fee is due with this response other than the fees indicated on the accompanying transmittal. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. MIN-P01-001 from which the undersigned is authorized to draw.

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Respectfully submitted,

By  _____

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